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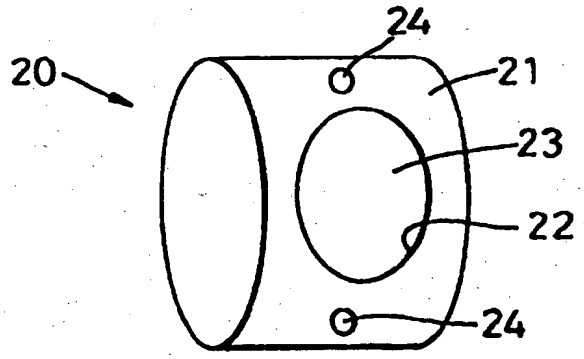
(57) Abstract

A microreactor (20) for the synthesis of chemical compounds includes a container having a body section (21). Entry pores are provided to permit fluid to enter the container and a visual identification device is provided to enable visual identification of the microreactor (20).



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"A Microreactor"

The invention relates to a microreactor, and especially a microreactor for synthesising chemical compounds.

Recent trends in the area of drug development, biotechnology and chemical research have moved towards producing large arrays of related molecules using combinatorial (or permutational) synthesis. These new techniques are potentially capable of yielding libraries of millions of compounds which can be screened, if a suitable assay is available, to identify the required properties, for example biological activity. The new methods have advantages because only a relatively small number of chemical reaction vessels need to be used, compared to the traditional methods in which a single compound is sequentially processed through various chemical transformations, usually one reaction step at a time. The new method, combinatorial synthesis, relies on the fact that under suitable conditions several compounds can be converted into several new products using a single reaction vessel.

The problems with combinatorial chemistry are manifold. First, reaction chemistry needs to be irreversible,

such that each of th starting materials in the mixture is converted to a n w product. Second, at the present time it is only feasible to perform combinatorial chemistry for large libraries in the "solid-phase", that is where the starting materials are covalently bonded to a polymeric support, which is usually cross-linked polystyrene. The advantages of solid-phase synthesis are that the products do not need to be purified by, for example, solvent extraction, distillation, recrystallisation or chromatography but rather are retained on the solid medium by washing away the excess reagents and impurities. Thus, in solid-phase synthesis (SPS) it is necessary to confine the polymeric support so that it too is not washed away.

The third problem concerns the deconvolution of the library which essentially requires identifying the chemical structure of the molecule, within the mixture, that shows the required biological activity or other desired property. Clearly, when one is dealing with mixtures of compounds, where the polymeric support for one compound looks identical to another requires the resynthesis of partial libraries of ever decreasing size, coupled with assay in order to identify the active material. This method of deconvolution is time consuming and unnecessarily clumsy. Another way of effecting deconvolution is to tag the polymeric support with chemicals which can be used to decode the synthetic chemical history of the particular particle of polymeric support, independently to being able to carry out an activity assay on the material attached to the support. Such methods have been described in the literature. Since typical particles of polymeric support are referred to as "resin beads" and are commercially available in the size 90-400 microns, deconvolution by such methods is a fiddly job requiring

accurate and expensiv instrumentation.

The fourth problem concerns checking th efficiency of the chemical synthesis and, in essence, this is a problem of scale. Individual beads possess, at most, only a few nanomoles of material attached to them and thus it is extremely difficult to check either the efficiency of the synthesis or the purity of the synthetic product. In highly sensitive biological screening assays this can be a very serious problem as the impurity could be responsible for a positive result. The best way to overcome this last problem is to perform syntheses on a larger scale such that some material can be put aside for characterisation and analysis. While this solution offers very many advantages, the practice of larger scale combinatorial syntheses requires the design and use of microreactors. To date, only two reports of the use of microreactors (or porous capsules) for solid-phase synthesis on a polymeric support have been described, and the authors supplied little information on the design of the microreactors. The main purpose of the reports was to describe the incorporation of an addressable microchip into the microreactors which could be written to and read using radio waves. This elegant idea does require the microreactors to be of a size large enough to contain the addressable chip, which in itself is not a problem, but again demands the use of sophisticated and expensive equipment for the identification of individual compounds.

In accordance with a first aspect of the present invention, a microreactor for synthesis of chemical compounds comprises a container comprising a body section; entry means to permit fluid to enter the container; and a visual identification device to enable

visual identification of the microreactor.

The term "microreactor" as used herein means a container comprising a material which is permeable to fluids. The container may enclose a solid material or particles on or with which reaction occurs, and the container is impermeable to the solid material or particles. Alternatively, the material of the container itself may comprise a chemically functionalised polymer on or with which reaction occurs. This can be referred to as a "bonded" microreactor.

The microreactor may further comprise a closure and the body section may have an opening, the closure being adapted to close the opening, and fluid being able to enter the container through the entry means when the opening is closed by the closure.

Alternatively, the body section may comprise a material which comprises a polymeric support on or with which reaction occurs. Typically, the polymeric support may be chemically functionalised polystyrene and may be in the form of a porus, frit or sintered material.

In accordance with a second aspect of the present invention, a method of identifying a microreactor for synthesis of chemical compounds comprises attaching a visual identification device to the microreactor to enable the microreactor to be visually identified.

An advantage of the invention is that it permits deconvolution of a library of synthesised molecules by visual identification of a microreactor.

Preferably, the visual identification device may

comprise a character and/or a colour. Typically, the charact r may b an alphanumeric charact r.

Typically, the visual identification device may be attached to the external surface of the container. However, alternatively, the visual identification device may be inserted into the container or may be incorporated into the material of the container, which may be the body section and/or the closure.

The closure may be removable or non-removable from the opening.

Typically, each microreactor may comprise a number of visual identification devices, which may be different or identical.

The visual identification devices may be attached to the microreactor prior to the microreactor being used for synthesis of chemical compounds. Alternatively, the visual identification devices may be attached as appropriate before or after each stage in the synthesis procedure, one at a time or several at a time.

The visual identification device may be of a size to be visually identified by humans, or alternatively may be identified by robotics or another type of machine.

Typically, a separate visual identification device is provided for each chemical in which the microreactor is immersed during synthesis.

In one example of the invention, the body section may have two openings and two removable closures, one closure for each opening. Typically, in this example of the invention, the body section may b tubular with

th openings provided at each end of th tubular body section.

In a second example of the invention, there may be just one opening in the body section, which may be cylindrical in form.

In the case of bonded microreactors which themselves consist of chemically functionalised frit glass or frit or foamed polymer, there do not need to be openings for loading and unloading of resin, as the chemically reactive groups would be retained within the bonded matrix itself.

Where the visual identification device is attached to the outer surface of the container, the device may comprise a ring shaped member which is fitted over the body section and visual identification may be provided by a colour of the member and/or by characters on the surface of the member.

Alternatively, the visual identification device may be inserted into holes or apertures in a side wall of the container. For example, the visual identification device may comprise a peg or bead which fits into and is held in the hole or aperture.

Preferably, the entry means is provided by apertures in the side walls of the container. The side walls may comprise frit material, a perforated polymer material or a mesh. It is possible that a combination of these materials could be used. Examples of suitable frit materials are frit glass, frit polyethylene, frit polypropylene and frit polytetrafluoroethylene (PTFE).

The closure may be attached to the body section by

b ing a push fit into the opening, by b ing thread dly connected to the body section or attached by an adhesive.

Typically, for biological applications, the microreactors may have a length of approximately 7-10mm, and internal width of 3.5-7mm and an outside width of 4-10mm. Typically, the microreactors are for use with standard commercially available polymer beads of 90-400 microns for solid support in the solid phase synthesis.

However, these dimensions should not be considered as being limiting and larger microreactors or smaller microreactors may be constructed for other applications. For example larger microreactors may be constructed and used for non-biological applications.

Typically, the microreactor and the visual identification device are composed of cheap inert material and the selection of the materials is dictated by the intended chemistry, ie only compatible materials are used, eg glass is not used with aqueous hydrofluoric acid and non-resistant polymers are not used with organic solvents.

Examples of a microreactor in accordance with the invention will now be described with reference to the accompanying drawings, in which:-

Fig. 1 is a cross sectional view through a first example of a microreactor;
Fig. 2 is a cross sectional view through a second example of a microreactor;
Fig. 3 is a perspective view of a third example of a microreactor;

Fig. 4 is a plan view of th microreactor shown in Fig. 3;

Fig. 5 is a front view of the microreactor shown in Fig. 3;

Fig. 6 is a back view of the microreactor shown in Fig. 3;

Fig. 7 is an exploded side view of a fourth example of a microreactor;

Fig. 8 is a side view of the microreactor of Fig. 7 assembled; and

Fig. 9 is a flow diagram illustrating how twenty-seven microreactors may be used to synthesise twenty-seven compounds from three suitably functionalised starting compounds.

Fig. 1 shows a first example of a microreactor 1 which comprises a polymer tube having 70 micron perforations in the wall of the tube 2. At each end of the tube 2 is an end cap 3. The material from which the tube 2 and end caps 3 are manufactured is inert with the compounds into which the microreactor 1 is to be immersed. Located within the microreactor 1 are a number of polymer beads 4 for solid support in solid phase synthesis. The polymer beads have a diameter which is greater than 70 microns.

A second example of a microreactor 5 is shown in Fig. 2. The microreactor 5 comprises a container body section 6 having an open end 7 which is closed by a removable lid 8. The container body section 6 and the removable lid 8 are both manufactured from frit glass and the frit glass is chosen to be inert with the compounds in which the microreactor 5 is to be immersed. However, any other suitable frit material may be used. The microreactor 5 also contains a number of polymer beads for solid support in solid phase

synth sis.

Figs. 3 to 6 show a third example of a microreactor 20 which is manufactured from a frit material. This may be frit glass, frit polyethylene, frit polytetrafluoroethylene or any other suitable frit material. A "suitable frit material" is any frit material which is inert with the chemicals into which the microreactor 20 is to be immersed.

The microreactor 20 consists of a cylindrical body section 21 which has a hole 22 drilled into the curved surface of the cylindrical body section 21. Hole 22 has polymer beads inserted into it before the hole 22 is plugged by a plug 23. Around the curved surface of the body section 21 a number of small holes 24 are drilled. These holes permit small coloured pegs to be attached to the microreactor 20 by being pushed into the holes 24.

After the hole 22 has been plugged by the plug 23, the plugged hole 22 forms a reaction chamber into which chemical fluids may enter through the holes in the frit material from which the body section 21 is formed. The plug 23 may be any suitable inert material, such as an inert polymer.

As an alternative to the microreactor 20, the microreactor could be manufactured from porous or frit perfluoroalkyl sulphonic acid resin, such as Nafion (trade mark) manufactured by Du Pont, so that the material of the microreactor itself forms the polymeric support. In addition, or alternatively, other chemically functionalised sintered, frit or porous polym rs or composites could b used to form the

In this example, th micror actor would not have the reaction chamber 22 or the closur 23 and would be a body of material porous or frit material. However, the holes 24 for the coloured pegs would still be present. The reactions then take place on or with the material of the microreactor itself.

Figs. 7 and 8 show a fourth example of a microreactor 30. Fig. 7 is an exploded side view of the microreactor 30 showing the components of the microreactor 30. The microreactor 30 has a tubular glass body 31 which has an external screw thread formation 32. The body 31 is hollow and two sealing rings 33 and a frit glass end closure 34 are secured to each end of the glass body 31 by an end cap 35. The end caps 35 are internally threaded so that they screw onto the thread 32 on the body 31.

If the end closures 34 are of a frit material, such as a plastic, it would not be necessary to use the sealing rings 33.

In use, one end cap 35, end closure 34 and sealing rings 33 are secured to one end of the body 31. The polymer beads may then be placed in the body 31 through the other open end. The open end is then closed using the other end cap 35, end closure 34 and sealing rings 33.

The visual identification devices for the microreactor 30 may be moulded into the end caps 35, which may be moulded from a plastics material. In addition, it is possible that the end caps 35 and/or body 31 may be individually colour coded.

In this example the body 31 is solid glass and not frit

glass.

Fig. 8 shows th ass mbl d micror actor 30. In the microreactor 30, the fluids enter the microreactor through the end closures 34 which are of a frit material, and therefore permeable to fluids but not to the polymer beads placed inside the microreactor 30.

Both frit glass tubes and rectangular chambers and perforated polymer tubes and meshes with appropriate lids were used as microreactors in the synthesis of small peptide libraries. Standard commercially available polymer beads 4 of 90-400 microns were used for the solid support in the solid phase synthesis (SPS). Essentially, the dimensions of the microreactors range from a length of 7-10mm, with an internal diameter of 3.5-7mm, and an outside diameter of 4-10mm, depending on the material. The walls of frit glass tube need to be thicker to provide mechanical strength. The lids 3, 8 of the microreactors 1, 5 and the plug 23 of the microreactor 20 are resistant polymer or frit glass and can be colour coded as part of the visually addressable system. The microreactors 1, 5, 20 themselves can also be colour coded or marked with the appropriate alpha-numeric or icon, or with multiple visual identifications. Larger microreactors can be constructed for non-biological applications using the same material and protocols outlined here.

The microreactors used were pre-labelled, that is the colours and alpha-numerics were already associated with each of the microreactors such that the chemical synthesis was programmed by the visual identification marks. In principle, this method offers no advantages or disadvantages in identification compared with

tagging the microreactors after each cycle of the synthesis. However, pre-labelled microreactors could be used in programmed robotic synthesis, where the machine or human readable identification is used to determine which vessel the microreactor is placed into for the next step. Another advantage is that microreactors could be manufactured and supplied in a coded form for the user to predetermine what each element of the code will mean in the synthesis of the chemical libraries. This also saves the user from needing to tag the microreactor after each step. Moreover, precision machine labelled microreactors have the potential to be smaller than those described above where for human visualisation, as opposed to robotic identification, the microreactor is read using a magnifying glass, typically of the type used by electronics engineers for identifying resistors and chips etc.

The limit of the number of sets of colours, alphanumerics, etc that can be read easily on the microreactors described above is six, without the aid of a magnifying glass. This number could be increased to twelve by precision manufacture of the microreactors for visual identification using a magnifying glass. However, in practise, twelve represents the number of actual synthetic steps (not counting chemical activation and protection and deprotection steps which support the synthetic chemistry) and twelve is probably beyond the need of any potential application other than bioactive peptide synthesis. The structural (molecular) diversity is limited by the visualisation method. For example, there are ten easily distinguishable colours and if all ten are used for each of six syntheses steps there are 10^6 individually addressable microreactors. For easily distinguishable

letters (of which there are 24, not counting Greek letters) there are 24^6 = 191 million addressable microreactors. For a two digit numeric labelling strategy there are 9.4148×10^{11} individually addressable microreactors. In practise these numbers are much larger than those required and typically libraries of microreactors would be 9-10,000 in size. Where the overall volume of each microreactor is 0.25-0.75 cm^3. a library of 10,000 compounds could be prepared easily in conventional laboratory scale equipment. Note that for a diversity factor of 10, ten separate reactions on 1000 compounds in 1000 microreactors would be performed in the last step to give a library of 10,000 compounds. 1000 microreactors would fit inside a vessel of 1000-2000 cm^3 and leave plenty of room for the solvent and mixing/heating/cooling and sensing equipment. Typical large scale laboratory equipment has a maximum capacity of 10,000 cm^3. Vessels larger than this require special facilities.

In a typical but non-restrictive protocol for peptide library or other compound library synthesis, a small amount of pre-swollen commercially available resin for solid phase peptide synthesis is added to the pre-labelled microreactor as a slurry in dimethylformamide such that the microreactor is half-full or less. A small glass bead or stirring magnet may be added to ensure thorough mixing. The microreactor, and any others which are to be processed, are placed in the main reaction vessel and are drowned in a solution of solvent eg dimethylformamide containing the appropriate reagents for either synthesis or deprotection in the usual way. The microreactors are physically agitated to ensure that each resin bead is exposed to the reagent solution. The microreactors are then transferred to

n w appropriate reaction vessels, togeth r with other microreactors, as dictated by the visually addressabl labels for further cycles of deprotection of synth sis. The entire process is repeated until the synthesis and deprotection is complete. The library of labelled microreactors is now ready for solid phase assay (on the polymer bead) where individual beads are removed to prepare a library or sub-library of beads of known composition. If solution phase assays are to be performed, the compounds are obtained by un-linking the polymer resin support. This can be performed either on the entire contents of any or all of the individual microreactors, or on just a portion of the contents. Unlinking is performed in the usual way. In our experiments we used Fmoc peptide chemistry and removed the compounds from the resin using trifluoroacetic acid. The purity and structure of the library members was assessed by nmr spectroscopy. Note that for unlabelled microreactors, one identification tag (eg a thin inert polymer ring or peg of a given colour or marked with a specific alphanumeric or icon) would be added either prior to, or, immediately after placement in a reaction vessel for every synthesis.

In the case of bonded microreactors composed of porous functionalised polymer, for example, perfluoroalkyl sulphonic acid or carboxylic acid resins such as Nafion or those manufactured by Asahi or Dow, the acid groups would be activated to load appropriate nucleophilic linker groups, for example, 3-aminobenzyl alcohol to give a chemical reaction surface similar to that for commercially available resins.

To illustrate how the visually interrogatable coding would work in the construction of a combinatorial library using permutational organic synthesis in

addressabl microreactors (POSAM), consider a library 10 of twenty-seven compounds made up from three structural moieties called A, B and C (see Fig. 9). Twenty-seven microreactors 11 are provided. In the first cycle of the reaction nine microreactors 11 are reacted with compound A, nine with B and nine with C, in separate vessels, to load the polymeric beads in the microreactors 11 with compounds A, B and C respectively. The microreactors 11 from each of the three vessels are then tagged with a visual identification mark such that the microreactors 11 loaded with A, B and C can be discriminated.

In the second cycle of synthesis, three of the microreactors 11 containing compound A, three containing B and three containing C are then reacted with compound A. When the reaction is complete the microreactors 11 are labelled with a further visually identifiable tag. Nine further microreactors 11 containing A, B and C (three of each) are then reacted with compound B and then tagged and the remaining nine microreactors 11 containing A, B and C are then reacted with compound C and then tagged. Thus there are now three sets 12 of nine differentially labelled microreactors containing the compounds AA, BA, CA, AB, BB, CB, AC, BC and CC (see Fig. 9).

In a third cycle, one set of the nine compounds is reacted with compound A, and then tagged and a further set of nine reacted with compound B, and then differentially tagged and finally, the last set of nine compounds is reacted with compound C and then tagged. This gives a final library of twenty-seven different compounds attached to the polymer support inside the twenty-seven microreactors 11 which are all individually distinguishable merely by looking at them.

Th visual identification of microreactors als ensures that no mistakes are mad during various cycles of library synth sis and avoids the statistical problems generated in the split and mix strategy that is used when dealing directly with the indistinguishable polymeric beads. If the synthetic efficiency of the chemical process needs to be interrogated, it is either possible to open up a microreactor and remove some of the material for analysis or to include extra identical microreactors visually tagged in the appropriate manner which are removed during the synthetic procedure, specifically for analysis.

The protocols described are suitable for a wide range of chemistries with reactors of a small size, as described here, up to quite large sizes eg 20 cm^3 per reactor. In industry and with special vessels even larger reactors could be used. Clearly, the larger the reactor the more easily it can be visually addressed. This patent should cover any confined solid support chemical reactor used to generate libraries of compounds greater than four members in two or more synthetic cycles either sequentially or simultaneously in larger reaction vessels where reactors are addressed by any visual interrogation system employing colour, alphabetic, numeric bar-coding or icon based system.

CLAIMS

1. A microreactor for synthesis of chemical compounds comprising a container comprising a body section; entry means to permit fluid to enter the container; and a visual identification device to enable visual identification of the microreactor.

2. A microreactor according to claim 1, wherein the body section comprises a body of material, the material comprising a polymeric support on or with which reaction occurs.

3. Apparatus according to claim 1, wherein the body section has an opening and the container further comprises a closure adapted to close the opening; and the entry means permits fluid to enter the container when the opening is closed by the closure.

4. A microreactor according to any of the preceding claims, wherein the visual identification device comprises a character and/or a colour.

5. A microreactor according to claim 4, wherein the character is an alphanumeric character.

6. A microreactor according to any of the preceding claims, wherein the visual identification device is attached to the external surface of the container.

7. A microreactor according to any of the preceding claims, wherein the visual identification device is incorporated into the material of the container.

8. A microreactor according to any of the preceding claims, wherein a microreactor comprises a number of

visual identification devices.

9. A microreactor according to any of the pr ceding claims, wherein the entry means is provided by apertures in the side walls of the container.

10. A microreactor according to claim 9, wherein the side walls of the container are porous.

11. A microreactor according to any of the preceding claims, wherein the visual identification device is inserted into holes or apertures in a side wall of the container to attach the visual identification device to the container.

12. A method of identifying a microreactor for synthesis of chemical compounds comprises attaching a visual identification device to the microreactor to enable the microreactor to be visually identified.

13. A method according to claim 12, wherein the visual identification devices are attached to the microreactor prior to the microreactor being used for synthesis of chemical compounds.

14. A method according to claim 12, wherein the visual identification devices are attached where appropriate before or after each stage in the synthesis procedure.

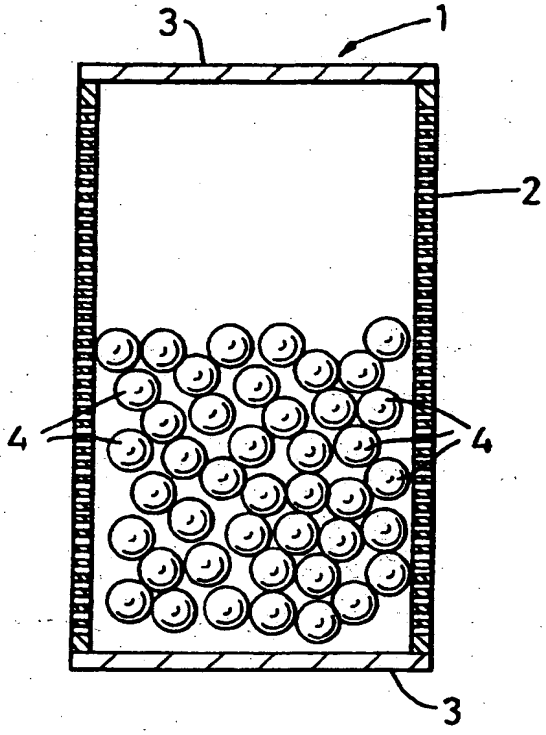

Fig. 1

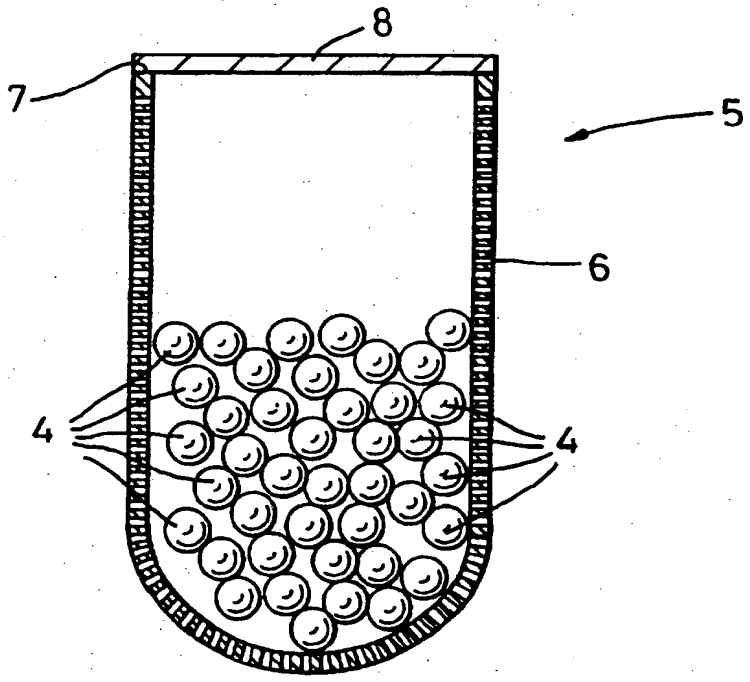

Fig. 2

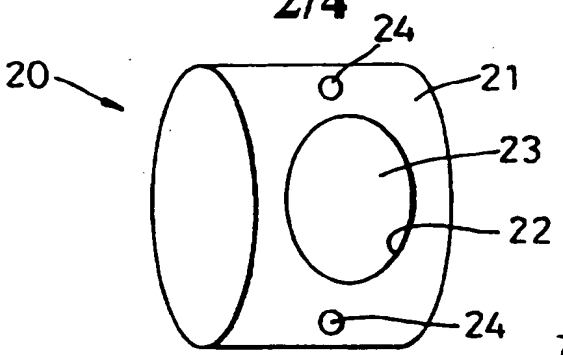

Fig. 3

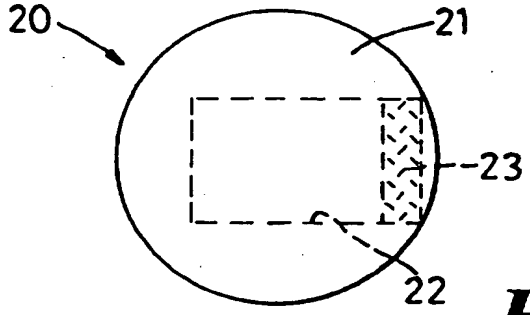

Fig. 4

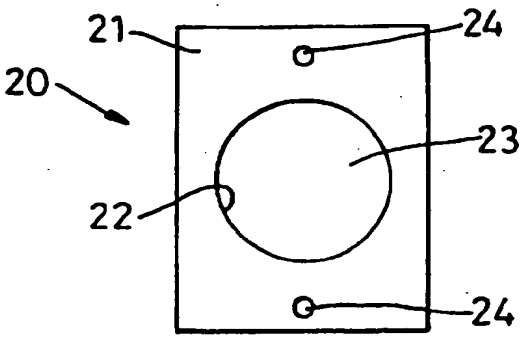

Fig. 5

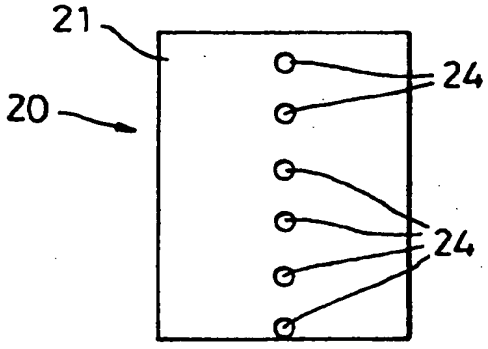

Fig. 6

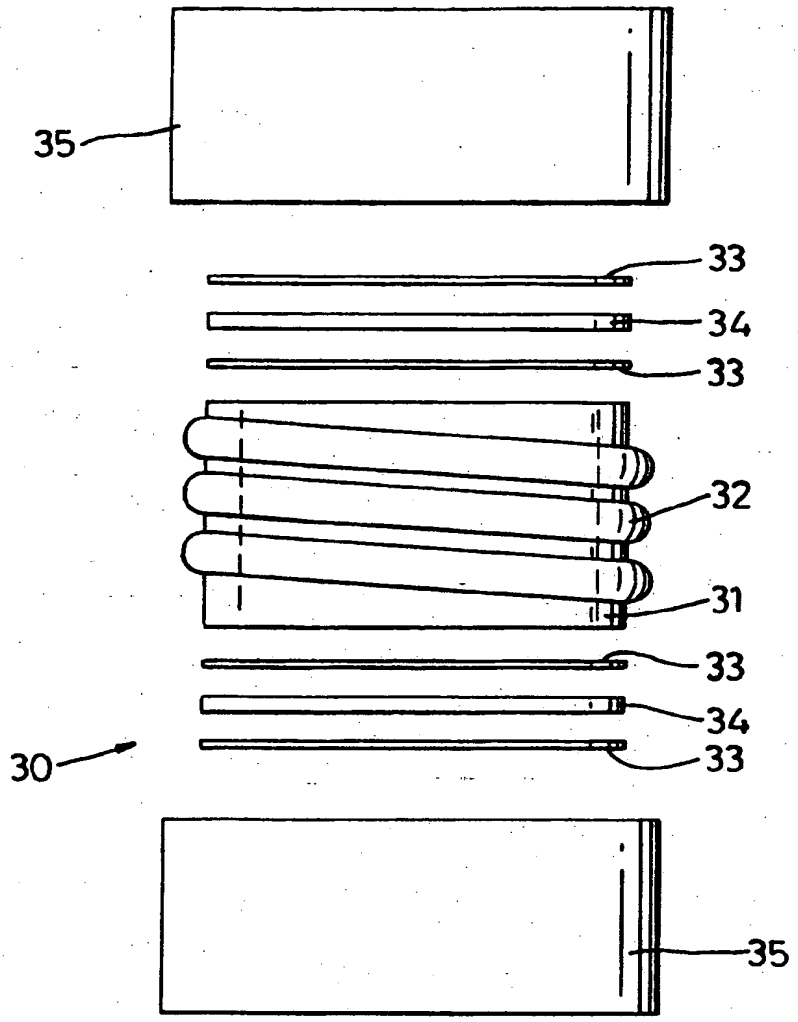

Fig. 7

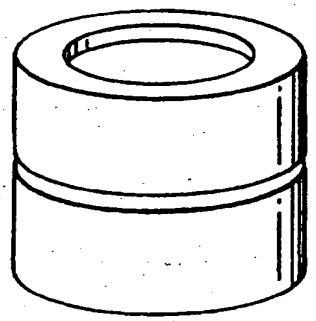

Fig. 8

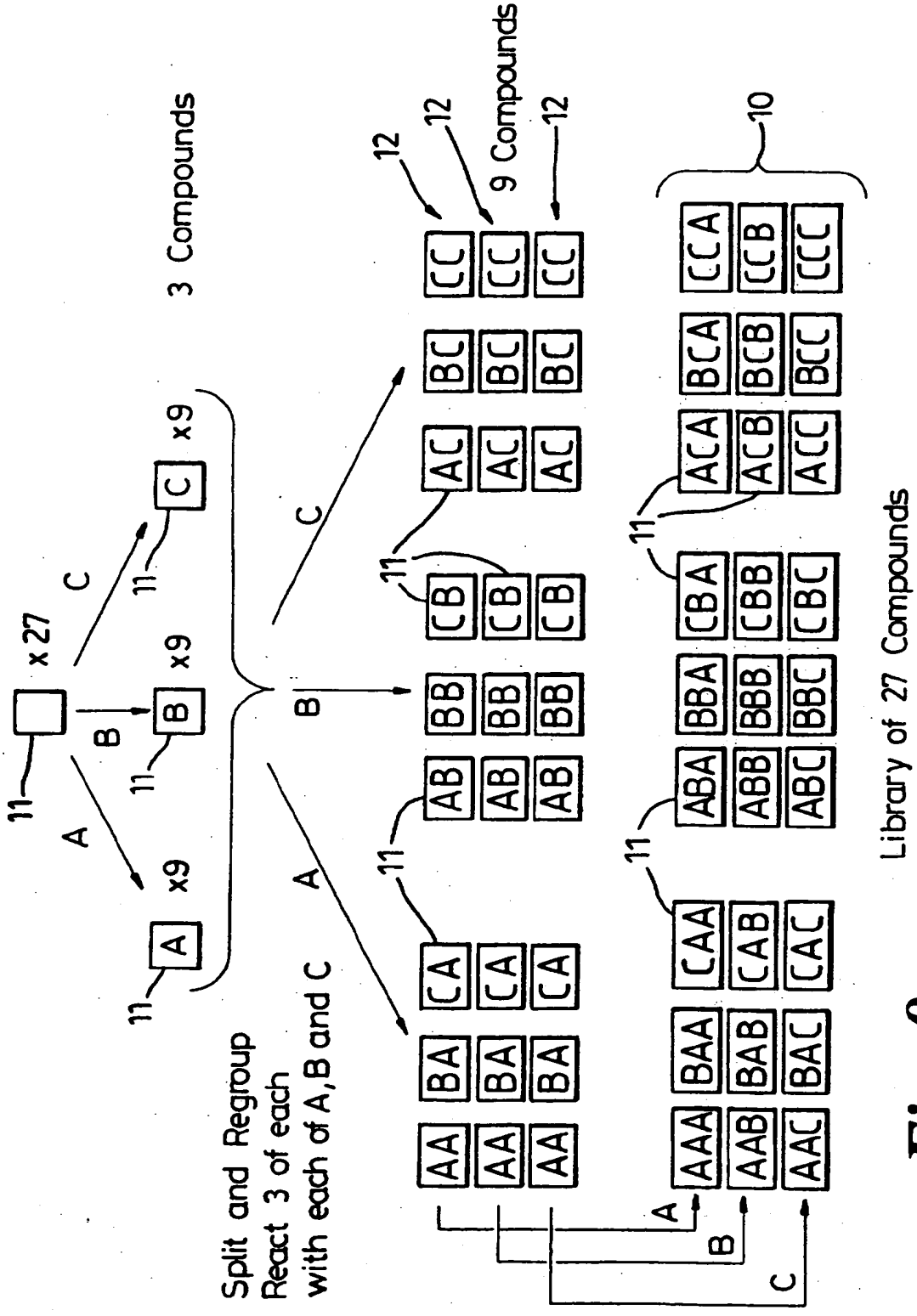
3 Compounds
9 Compounds
Library of 27 Compounds
Split and Regroup
React 3 of each
with each of A,B and C
x 27
x9
x9
x9
A
B
C
11
12
10

Fig. 9

INTERNATIONAL SEARCH REPORT

Interr ul Application No
PCT/GB 97/00496

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 B01J19/00 C07K1/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C12M B01J C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	EP 0 156 588 A (APPLIED BIOSYSTEMS) 2 October 1985 see page 40 - page 42; claims 1-6; figures 1-5	1-10, 12-14 1-11
Y	EP 0 196 174 A (SCRIPPS CLINIC RES) 1 October 1986 see page 21; figure 5B	11
Y	FR 2 526 169 A (MOCHIDA PHARM CO LTD) 4 November 1983 see claims; figures	1,2,4-8

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 June 1997	01.07.97

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Coucke, A

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INTERNATIONAL SEARCH REPORT

Intern nal Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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INTERNATIONAL SEARCH REPORT

...formation on patent family members

Inter ...nal Application No
PCT/GB 97/00496

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